

SPECIFICATION

A PROCESS FOR PRODUCING AN AROMATIC UNSATURATED COMPOUND

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TECHNOLOGICAL FIELD

The present invention relates to a process for producing an aromatic unsaturated compound.

10 BACKGROUND TECHNOLOGY

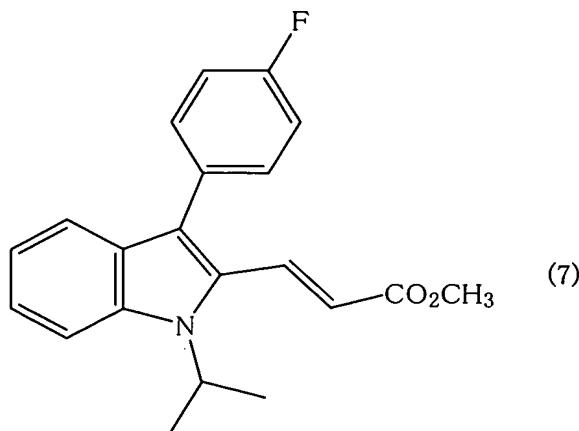
An aromatic unsaturated compound of the formula (4)



wherein Ar represents an optionally substituted aromatic group or an optionally substituted heteroaromatic group, and Y represents an

15 electron withdrawing group (hereinafter, abbreviated as aromatic unsaturated compound (4))

is useful as, for example, a synthetic intermediate of medical and agricultural chemicals or the like. For example, a compound of the following formula (7)

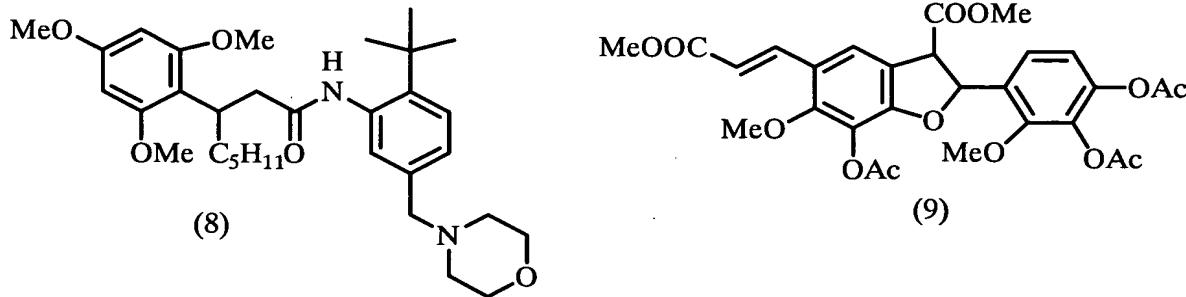


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is known as a synthetic intermediate of fluvastatin useful as a hyperlipidemia drug as described also in, for example, WO 01/92223.

Compounds of the following formulae (8) and (9) are compounds being developed as an arteriosclerosis remedy as described also in

5 JPH09-202775-A and JPH07-206842-A, respectively.



As a process for producing such an aromatic unsaturated compound (4), there is known, for example, a process reacting an aromatic halide with an acrylic acid compound such as acrylic acid and the like in the presence of a palladium catalyst and a base (for example, WO 01/92223), however, an aromatic halide manifesting high load on environments is required to be used as a raw material, and additionally, a hydrogen halide is by-produced together with progress of the reaction. In addition, since the above-mentioned hydrogen halide is required to be neutralized with a base, it is not necessarily a reaction of high atom economy from the standpoint of raw material.

On the other hand, as a process of higher atom economy, there is a process using a compound of the formula (1)



20 wherein, Ar is as defined above,

as a raw material and reacting it with an acrylic acid compound. For example, there are suggested (a) a process using a ruthenium catalyst and a palladium catalyst and reacting in the presence of oxygen (for example, J. Am. Chem. Soc., 125, 1467 (2003), J. Am. Chem. Soc., 123, 337

(2001)), (b) a process using a palladium complex in an amount equal to or more than the theoretical amount (for example, J. Org. Chem., 46, 851 (1981), Heterocycles, 22, 1493 (1984)), and the like.

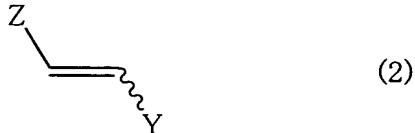
However, the process (a) is not necessarily advantageous from the standpoint of operation and equipments since oxygen is used and accordingly the process is required to be performed under the reaction condition not higher than the explosion limit. The process (b) is disadvantageous from the standpoint of cost since a palladium complex in an amount equal to or more than the theoretical amount is used though it is a method of higher atom economy from the standpoint of raw material. In addition, post treatment of the palladium complex after the reaction is troublesome, further, the yield is low. That is, it is not necessarily an advantageous method from the standpoint of industrial production.

As a process for producing a compound having an indole ring, there is known a process protecting a nitrogen atom constituting an indole ring with a benzenesulfonyl group, then, reacting it with an acrylic acid compound in the presence of a palladium catalyst (for example, Synthesis, 236 (1984)). This process, however, is a reaction limited to a compound in which a nitrogen atom constituting an indole ring is protected with a benzenesulfonyl group, and additionally, needs a use in excess amount of a relatively expensive re-oxidizer such as, for example, silver acetate and the like for obtaining an intended object in good yield.

25 SUMMARY OF THE INVENTION

Under such conditions, the present inventors have intensively studied for developing a process for producing the above-mentioned aromatic unsaturated compound (4) with higher atom economy and more advantageously from industrial standpoint using a compound of the

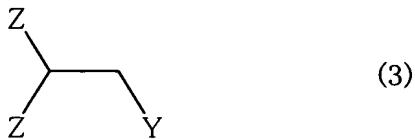
above-mentioned formula (1) as a raw material and resultantly found that the object of the instant application can be attained by reacting a compound of the above-mentioned formula (1) with a compound of the formula (2)



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wherein Y represents an electron withdrawing group, and Z represents a lower alkoxy group,

or with a compound of the formula (3)



10 wherein, Y and Z have the same meanings as defined above, in the presence of an acid such as hydrochloric acid and the like, or a compound capable of generating a mineral acid by its hydrolysis such as phosphorus oxychloride and the like, leading to completion of the present invention.

15 That is, the present invention includes the following inventions.

<1> A process for producing an aromatic unsaturated compound of the formula (4)

which comprises reacting (a) a compound of the formula (1) with (b) a compound of the formula (2) or a compound of the formula (3) in the

20 presence of (c) an acid or a compound which generates a mineral acid by its hydrolysis.

<2> The process according to <1>, wherein the reaction is conducted in the co-presence of water.

<3> The process according to <1> or <2>, wherein (c) an acid or a

25 compound which generates a mineral acid by its hydrolysis is hydrogen

halide.

<4> The process according to <1> or <2>, wherein (c) an acid or a compound which generates a mineral acid by its hydrolysis is phosphorus oxyhalide, phosphorus halide, thionyl halide or sulfonyl halide.

5 <5> The process according to any of <1> to <4>, wherein the reaction is conducted in acetic acid.

<6> The process according to any of <1> to <5>, wherein Ar in the formulae (1) and (4) is an aromatic group or a heteroaromatic group which may be substituted by at least one group selected from the group

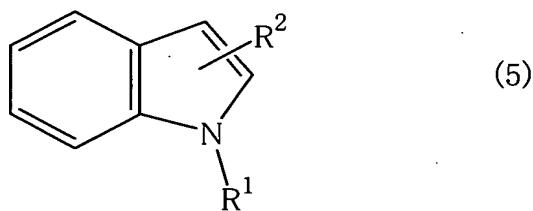
10 consisting of a lower alkyl, a lower alkoxy, a hydroxyl, -OR^x, an amino, -NHR^y, -NR^y₂, halogen and a phenyl optionally substituted by halogen(s),

wherein R^x represents a protective group of hydroxyl and R^y represents a protective group of amino.

15 <7> The process according to any of <1> to <6>, wherein Ar in the formulae (1) and (4) is an optionally substituted phenyl.

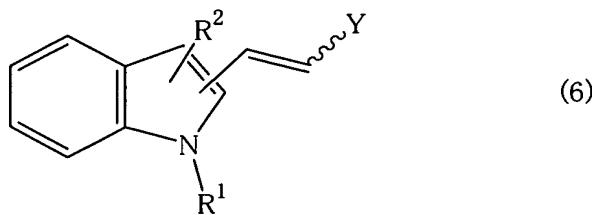
<8> The process according to any of <1> to <6>, wherein Ar in the formulae (1) and (4) is an optionally substituted indolyl.

19 <9> The process according to any of <1> to <6> or <8>, wherein the compound of the formula (1) is a compound of the formula (5)



wherein R¹ represents a phenyl optionally substituted by halogen(s), a hydrogen or an alkyl and R² represents an alkyl or a phenyl optionally substituted by halogen(s), and

25 the compound of the formula (4) is a compound of the formula (6)



wherein R^1 and R^2 have the same meanings as defined above.

BEST MODES FOR CARRYING OUT THE INVENTION

protected with a protective group represented by -OR^x; aminos protected with a protective group represented by -NHR^y or -NR^y₂; halogens such as fluorine, chlorine, bromine, iodine and the like; phenyls optionally substituted with a halogen such as phenyl,

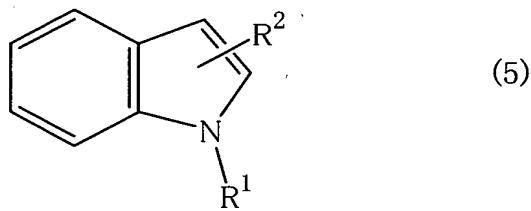
- 5 4-chlorophenyl, 4-fluorophenyl, and the like. Examples of the protective group on a hydroxyl group represented by R^x include alkanoyls such as acetyl and the like; alkoxyalkyls such as methoxymethyl and the like; aralkyls such as benzyl and the like; alkynes such as methylene, dimethylmethylenes and the like, and
- 10 examples of hydroxyl groups protected with such a protective group represented by -OR^x include acetoxy, methoxymethoxy, benzyloxy, methylenedioxy, dimethylmethylenedioxy and the like. Examples of the protective group on amino represented by R^y include the above-mentioned alkanoyls; aralkyls such as benzyl and the like;
- 15 aralkyloxyalkyls such as benzyloxymethyl and the like; dialkoxyalkyls such as dimethoxymethyl and the like; sulfonyls such as benzenesulfonyl, p-toluenesulfonyl, methanesulfonyl and the like, and examples of aminos protected with such a protective group represented by -NHR^y or -NR^y₂ include acetylarnino, dibenzylarnino, dibenzyloxymethylarnino,
- 20 dimethoxymethylarnino, benzenesulfonylarnino, p-toluenesulfonylarnino, methanesulfonyl amino and the like.

In the case of aromatic groups substituted with such a substituent, the number of such substituents is not particularly limited, however, aromatic groups substituted with two or more electron donating

- 25 substituents are preferable, and aromatic groups substituted with three or more electron donating substituents are more preferable, from the standpoint of reaction speed. Also in the case of heteroaromatic groups substituted with a substituent, the number of such substituents is not particularly limited, however, heteroaromatic groups substituted with at

least one electron donating substituents are preferable, from the standpoint of reaction speed. The electron donating substituent herein referred to indicates an alkyl, lower alkoxy having 1 to 4 carbon atoms, hydroxyl group, hydroxyl group protected with a protective group represented by $-OR^x$, amino, or amino protected with a protective group represented by $-NHR^y$ or $-NR^y_2$, among the above-mentioned substituents.

Among such compounds (1), compounds in which the heteroaromatic group is an indolyl group are important since they are synthetic raw materials of indole compounds such as, for example, fluvastatin and the like useful as a hyperlipidemia drug (e.g., JPH02-46031-B, WO01/92223, and the like), and examples of such compounds in which the heteroaromatic group is an indolyl group include compounds of the formula (5)



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wherein, R^1 represents a phenyl optionally substituted with halogen(s), or represents hydrogen or alkyl, and R^2 represents an alkyl, or represents a phenyl optionally substituted with halogen(s).

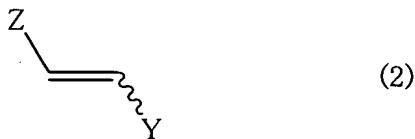
In the above-mentioned formula (5), the phenyl optionally substituted with halogen(s) includes the same moieties as described above, and examples of the alkyl include alkyls having 1 to 6 carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-hexyl and the like.

Examples of such compounds (1) include benzene, naphthalene, dimethoxybenzene, 1,3,5-trimethoxybenzene, 1,2,3-trimethoxybenzene, 2,6-dimethoxyphenol, 2-methoxyaniline, 4-methoxyaniline,

- 2-methoxyacetanilide, 4-methoxyacetanilide, 2-acetylaminophenol,
 4-acetylaminophenol, catechol, resorcinol, hydroquinone,
 4-tert-butylcatechol, capsaicin, 2-methyl-1H-indole,
 2-methyl-1-methyl-1H-indole, 2-methyl-1-isopropyl-1H-indole,
 5 2-methyl-1-phenyl-1H-indole, 2-ethyl-1H-indole,
 2-ethyl-1-methyl-1H-indole, 2-ethyl-1-phenyl-1H-indole,
 2-phenyl-1H-indole, 2-phenyl-1-methyl-1H-indole,
 2-phenyl-1-phenyl-1H-indole, 3-methyl-1H-indole,
 3-methyl-1-methyl-1H-indole, 3-methyl-1-isopropyl-1H-indole,
 10 3-methyl-1-phenyl-1H-indole, 3-ethyl-1H-indole,
 3-ethyl-1-methyl-1H-indole, 3-ethyl-1-phenyl-1H-indole,
 3-phenyl-1H-indole, 3-phenyl-1-methyl-1H-indole,
 3-phenyl-1-phenyl-1H-indole, 3-(4-fluorophenyl)-1-isopropyl-1H-indole,
 and the like.

15 As such compounds (1), commercially available compounds may be used, and those produced according to known methods may also be used. For example, a compound in which the aromatic group is an indolyl group can be produced according to known methods such as, for example, *Tetrahedron Letters*, 26, 2155 (1985) and the like.

20 In a compound of the formula (2)



hereinafter abbreviated as compound (2), and a compound of the formula (3)



25 hereinafter abbreviated as compound (3), Y represents an electron

withdrawing group, and Z represents a lower alkoxy.

Examples of the electron withdrawing group include alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, acyl, cyano and the like.

Examples of the alkoxycarbonyl include alkoxycarbonyls having 2 to 9

- 5 carbon atoms such as methoxycarbonyl, ethoxycarbonyl,
n-propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl,
isobutoxycarbonyl, tert-butoxycarbonyl, n-hexyloxycarbonyl,
n-octyloxycarbonyloxy and the like. Examples of the aryloxycarbonyl
include aryloxycarbonyls having 7 to 13 carbon atoms such as
10 phenoxy carbonyl, and the like, and examples of the aralkyloxycarbonyl
include aralkyloxycarbonyls having 8 to 14 carbon atoms such as
benzyloxycarbonyl, and the like. Examples of the acyl include
aliphatic acyls having 2 to 9 carbon atoms such as acetyl, propionyl and
the like; aromatic acyls having 7 to 13 carbon atoms such as benzoyl, and
15 the like. Examples of the lower alkoxy include alkoxy's having 1 to 6
carbon atoms such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy,
isobutoxy, sec-butoxy, tert-butoxy, n-pentyloxy, n-hexyloxy and the like,
and preferable are alkoxy's having 1 to 4 carbon atoms.

Examples of such compounds (2) include methyl 3-methoxyacrylate,

- 20 ethyl 3-methoxyacrylate, n-propyl 3-methoxyacrylate, isopropyl
3-methoxyacrylate, n-butyl 3-methoxyacrylate, isobutyl
3-methoxyacrylate, sec-butyl 3-methoxyacrylate, tert-butyl
3-methoxyacrylate, phenyl 3-methoxyacrylate, benzyl 3-methoxyacrylate,
methyl 3-ethoxyacrylate, ethyl 3-ethoxyacrylate, n-propyl
25 3-ethoxyacrylate, isopropyl 3-ethoxyacrylate, n-butyl 3-ethoxyacrylate,
isobutyl 3-ethoxyacrylate, sec-butyl 3-ethoxyacrylate, tert-butyl
3-ethoxyacrylate, phenyl 3-ethoxyacrylate, benzyl 3-ethoxyacrylate,
methyl 3-isopropoxyacrylate, ethyl 3-isopropoxyacrylate, n-propyl
3-isopropoxyacrylate, isopropyl 3-isopropoxyacrylate, n-butyl

- 3-isopropoxyacrylate, isobutyl 3-isopropoxyacrylate, sec-butyl
3-isopropoxyacrylate, tert-butyl 3-isopropoxyacrylate, phenyl
3-isopropoxyacrylate, benzyl 3-isopropoxyacrylate, methyl
3-n-butoxyacrylate, ethyl 3-n-butoxyacrylate, n-propyl
5 3-n-butoxyacrylate, isopropyl 3-n-butoxyacrylate, n-butyl
3-n-butoxyacrylate, isobutyl 3-n-butoxyacrylate, sec-butyl
3-n-butoxyacrylate, tert-butyl 3-n-butoxyacrylate, phenyl
3-n-butoxyacrylate, benzyl 3-n-butoxyacrylate, methyl
3-tert-butoxyacrylate, ethyl 3-tert-butoxyacrylate, n-propyl
10 3-tert-butoxyacrylate, isopropyl 3-tert-butoxyacrylate, n-butyl
3-tert-butoxyacrylate, isobutyl 3-n-butoxyacrylate, sec-butyl
3-tert-butoxyacrylate, tert-butyl 3-tert-butoxyacrylate, phenyl
3-tert-butoxyacrylate, benzyl 3-tert-butoxyacrylate,
3-methoxyacrylonitrile, 3-ethoxyacrylonitrile, 3-isopropoxyacrylonitrile,
15 3-n-butoxyacrylonitrile, 3-tert-butoxyacrylonitrile,
4-methoxy-3-buten-2-one, 4-ethoxy-3-buten-2-one,
3-methoxy-1-phenylpropenone and the like.

In the compound (2), a trans isomer and cis isomer exists, and any one of them may be used or any mixture of them may be used in the
20 present invention.

Examples of the compound (3) include methyl
3,3-dimethoxypropionate, ethyl 3,3-dimethoxypropionate, n-propyl
3,3-dimethoxypropionate, isopropyl 3,3-dimethoxypropionate, n-butyl
3,3-dimethoxypropionate, isobutyl 3,3-dimethoxypropionate, sec-butyl
25 3,3-dimethoxypropionate, tert-butyl 3,3-dimethoxypropionate, phenyl
3,3-dimethoxypropionate, benzyl 3,3-dimethoxypropionate, methyl
3,3-diethoxypropionate, ethyl 3,3-diethoxypropionate, n-propyl
3,3-diethoxypropionate, isopropyl 3,3-diethoxypropionate, n-butyl
3,3-diethoxypropionate, isobutyl 3,3-diethoxypropionate, sec-butyl

- 3,3-diethoxypropionate, tert-butyl 3,3-diethoxypropionate, phenyl
3,3-diethoxypropionate, benzyl 3,3-diethoxypropionate, methyl
3,3-diisopropoxypropionate, ethyl 3,3-diisopropoxypropionate, n-propyl
3,3-diisopropoxypropionate, isopropyl 3,3-diisopropoxypropionate,
5 n-butyl 3,3-diisopropoxypropionate, isobutyl
3,3-diisopropoxypropionate, sec-butyl 3,3-diisopropoxypropionate,
tert-butyl 3,3-diisopropoxypropionate, phenyl
3,3-diisopropoxypropionate, benzyl 3,3-diisopropoxypropionate, methyl
3,3-di(n-butoxy)propionate, ethyl 3,3-di(n-butoxy)propionate, n-propyl
10 3,3-di(n-butoxy)propionate, isopropyl 3,3-di(n-butoxy)propionate,
n-butyl 3,3-di(n-butoxy)propionate, isobutyl 3,3-di(n-butoxy)propionate,
sec-butyl 3,3-di(n-butoxy)propionate, tert-butyl
3,3-di(n-butoxy)propionate, phenyl 3,3-di(n-butoxy)propionate, benzyl
3,3-di(n-butoxy)propionate, methyl 3,3-di(tert-butoxy)propionate, ethyl
15 3,3-di(tert-butoxy)propionate, n-propyl 3,3-di(tert-butoxy)propionate,
isopropyl 3,3-di(tert-butoxy)propionate, n-butyl
3,3-di(tert-butoxy)propionate, isobutyl 3,3-di(tert-butoxy)propionate,
sec-butyl 3,3-di(tert-butoxy)propionate, tert-butyl
3,3-di(tert-butoxy)propionate, phenyl 3,3-di(tert-butoxy)propionate,
20 benzyl 3,3-di(tert-butoxy)propionate, 3,3-dimethoxypropionitrile,
3,3-diethoxypropionitrile, 3,3-diisopropoxypropionitrile,
3,3-di(n-butoxy)propionitrile, 3,3-di(tert-butoxy)propionitrile,
1,1-dimethoxy-3-butanone, 1,1-diethoxy-3-butanone,
3,3-dimethoxy-1-phenylpropan-1-one, and the like.
- 25 As such compounds (2) and compounds (3), commercially available compounds may be used, and those produced according to known method, such as JPS61-45974-B, JPS58-26855-A and the like may also be used.

The amount used of the compound (2) or compound (3) is usually 1 to 5 mol, preferably 1 to 3 mol in total based on 1 mol of the compound

(1).

Examples of the acid include sulfuric acid; hydrochloric acid; hydrogen halides such as hydrogen bromide and the like; perhalogenic acids such as perchloric acid; sulfonic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, trifluoromethanesulfonic acid and the like; perfluorocarboxylic acids such as trifluoroacetic acid and the like; aprotic acids such as boron trifluoride, aluminum chloride, aluminum bromide, zinc chloride, zinc bromide, tin chloride, titanium tetrachloride and the like; acidic ion exchange resins and the like, and preferable are hydrogen halides. As the aprotic acid, complexes of aprotic acids such as, for example, a boron trifluoride•tetrahydrofuran complex and the like may also be used. In the method of the present invention, when the acid to be used is a protonic acid, acids having a pKa of 2.5 or less are preferred, and acids having a pKa of 1.5 or less are more preferred.

Examples of the compound capable of generating a mineral acid by hydrolysis (hereinafter, may be referred to as MAGH compound) include phosphorus oxyhalides such as phosphorus oxychloride, phosphorus oxybromide and the like; phosphorus halides such as phosphorus trichloride, phosphorus tribromide, phosphorus pentachloride and the like; thionyl halides such as thionyl chloride and the like; sulfonyl halides such as sulfonyl chloride, and the like, and preferable are phosphorus oxyhalides.

A compound (1) may be reacted with a compound (2) or a compound (3) in the presence of an acid, or a compound (1) may be reacted with a compound (2) or a compound (3) in the presence of a MAGH compound. Alternatively, a compound (1) may also be reacted with a compound (2) or a compound (3) in the presence of an acid and MAGH compound.

The mixing order of them is not particularly limited, and for

example, an acid or MAGH compound may be added to a mixture of a compound (1) and a compound (2) or a compound (3), or a compound (2) or a compound (3) may be added to a mixture of a compound (1) and an acid or MAGH compound.

- 5 The amount used of an acid or MAGH compound is usually 0.001 mol or more, preferably 0.01 mol or more in total based on 1 mol of the compound (1), the upper limit thereof is not particularly set, and in the case of liquid under reaction conditions, it may be used in excess amount for acting also as a solvent, and the amount is practically 5 mol or less, 10 preferably 3 mol or less from the standpoint of post treatment and economy.

The reaction is performed usually in the presence of a solvent, and examples of the solvent include nitrile-based solvents such as acetonitrile, propionitrile and the like, carboxylic acid-based solvents 15 such as formic acid, acetic acid and the like, halogenated hydrocarbon-based solvents such as dichloromethane, chloroform and the like, ether-based solvents such as tetrahydrofuran and the like, ester-based solvents such as ethyl acetate and the like, alcohol-based solvents such as methanol, ethanol, isopropanol and the like, water, and 20 the like, which may be single solvent or mixed solvent, and preferable are carboxylic acid-based solvents and nitrile-based solvents, and more preferable are carboxylic acid-based solvents, and among them, acetic acid is particularly preferable. The amount used of such solvents is not particularly limited. As described above, when the above-mentioned 25 acid or MAGH compound is liquid under reaction conditions, such an acid or MAGH compound may be used as a solvent.

The intended aromatic unsaturated compound (4) can be obtained by reacting a compound (1) with a compound (2) or compound (3) in the presence of an acid or MAGH compound. The aromatic unsaturated

compound (4) can be obtained with better yield by carrying out the reaction in the coexistence of water.

The amount used of water when the reaction is carried out in the coexistence of water is usually 0.1 mol or more based on 1 mol of the compound (1), and though its upper limit is not particularly limited, it is practically 50 mol or less, preferably 10 mol or less.

The reaction temperature is usually -20 to 80°C.

After completion of the reaction, the intended aromatic unsaturated compound (4) can be taken out by, for example, filtration treatment, after mixing the reaction liquid with water. In a certain case, the aromatic unsaturated compound (4) precipitates as crystals in the reaction liquid. In such a case, the aromatic unsaturated compound (4), may be taken out directly by filtration treatment of the reaction liquid, or by filtration treatment after mixing the reaction liquid and water. Alternatively, the compound (4) may also be taken out, for example, by adding water and water-insoluble organic solvent such as toluene, ethyl acetate, methyl t-butyl ether, methyl isobutyl ketone and the like to the reaction liquid, extracting the mixture, and concentrating the resulting organic layer. The obtained aromatic unsaturated compound (4) may further be purified by conventional purification means such as, for example, recrystallization, column chromatography and the like.

Examples of thus obtained aromatic unsaturated compound (4) include methyl 3-(2,4,6-trimethoxyphenyl)acrylate, methyl 3-(2,3,4-trimethoxyphenyl)acrylate, methyl 3-(3-hydroxy-2,4-dimethoxyphenyl)acrylate, methyl 3-(3,4-dihydroxyphenyl)acrylate, ethyl 3-(2,4,6-trimethoxyphenyl)acrylate, ethyl 3-(2,3,4-trimethoxyphenyl)acrylate, ethyl 3-(3-hydroxy-2,4-dimethoxyphenyl)acrylate, ethyl

- 3-(3,4-dihydroxyphenyl)acrylate, n-propyl
3-(2,4,6-trimethoxyphenyl)acrylate, n-propyl
3-(2,3,4-trimethoxyphenyl)acrylate, n-propyl
3-(3-hydroxy-2,4-dimethoxyphenyl)acrylate, n-propyl
5 3-(3,4-dihydroxyphenyl)acrylate, isopropyl
3-(2,4,6-trimethoxyphenyl)acrylate, isopropyl
3-(2,3,4-trimethoxyphenyl)acrylate, isopropyl
3-(3-hydroxy-2,4-dimethoxyphenyl)acrylate, isopropyl
3-(3,4-dihydroxyphenyl)acrylate, n-butyl
10 3-(2,4,6-trimethoxyphenyl)acrylate, n-butyl
3-(2,3,4-trimethoxyphenyl)acrylate, n-butyl
3-(3-hydroxy-2,4-dimethoxyphenyl)acrylate, n-butyl
3-(3,4-dihydroxyphenyl)acrylate, isobutyl
3-(2,4,6-trimethoxyphenyl)acrylate, isobutyl
15 3-(2,3,4-trimethoxyphenyl)acrylate, isobutyl
3-(3-hydroxy-2,4-dimethoxyphenyl)acrylate, isobutyl
3-(3,4-dihydroxyphenyl)acrylate, phenyl
3-(2,4,6-trimethoxyphenyl)acrylate, phenyl
3-(2,3,4-trimethoxyphenyl)acrylate, phenyl
20 3-(3-hydroxy-2,4-dimethoxyphenyl)acrylate, phenyl
3-(3,4-dihydroxyphenyl)acrylate, benzyl
3-(2,4,6-trimethoxyphenyl)acrylate, benzyl
3-(2,3,4-trimethoxyphenyl)acrylate, benzyl
3-(3-hydroxy-2,4-dimethoxyphenyl)acrylate, benzyl
25 3-(3,4-dihydroxyphenyl)acrylate,
3-(2,4,6-trimethoxyphenyl)acrylonitrile,
3-(2,3,4-trimethoxyphenyl)acrylonitrile,
3-(3-hydroxy-2,4-dimethoxyphenyl)acrylonitrile,
3-(3,4-dihydroxyphenyl)acrylonitrile,

- 4-(2,4,6-trimethoxyphenyl)-3-buten-2-one,
4-(2,3,4-trimethoxyphenyl)-3-buten-2-one,
4-(3-hydroxy-2,4-dimethoxyphenyl)-3-buten-2-one,
4-(3,4-dihydroxyphenyl)-3-buten-2-one,
- 5 3-(2,3,4-trimethoxyphenyl)-1-phenylpropenone,
3-(3-hydroxy-2,4-dimethoxyphenyl)-1-phenylpropenone,
3-(3,4-dihydroxyphenyl)-1-phenylpropenone, methyl
3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylate, ethyl
3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylate, n-propyl
- 10 3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylate, isopropyl
3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylate, n-butyl
3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylate, isobutyl
3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylate, tert-butyl
3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylate, phenyl
- 15 3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylate, benzyl
3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylate,
3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylonitrile, methyl
3-(1-methyl-2-phenyl-1H-indol-3-yl)acrylate, ethyl
3-(1-methyl-2-phenyl-1H-indol-3-yl)acrylate, n-propyl
- 20 3-(1-methyl-2-phenyl-1H-indol-3-yl)acrylate, isopropyl
3-(1-methyl-2-phenyl-1H-indol-3-yl)acrylate, n-butyl
3-(1-methyl-2-phenyl-1H-indol-3-yl)acrylate, isobutyl
3-(1-methyl-2-phenyl-1H-indol-3-yl)acrylate, tert-butyl
3-(1-methyl-2-phenyl-1H-indol-3-yl)acrylate, phenyl
- 25 3-(1-methyl-2-phenyl-1H-indol-3-yl)acrylate, benzyl
3-(1-methyl-2-phenyl-1H-indol-3-yl)acrylate,
3-(1-methyl-2-phenyl-1H-indol-3-yl)acrylonitrile,
4-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]-3-buten-2-one,
4-(1-methyl-2-phenyl-1H-indol-3-yl)-3-buten-2-one,

3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]-1-phenylpropanone, 3-(1-methyl-2-phenyl-1H-indol-3-yl)-1-phenylpropanone, and the like.

In this reaction, both when a trans isomer is used and when a cis isomer is used as the compound (2), there are usually obtained a trans 5 isomer of an aromatic unsaturated compound (4) or a trans-cis isomer mixture of an aromatic unsaturated compound (4) containing mainly a trans isomer.

Of such aromatic unsaturated compounds (4), compounds having a 10 3-(4-fluorophenyl)indolyl group in its molecule represented by, for example, the following formula (7) and the like can be converted into fluvastatin useful as a hyperlipidemia drug according to, for example, a 15 method of WO 01/92223.

The present invention will be illustrated further in detail by the following examples, but the scope of the invention is not limited to these 15 examples.

Example 1

1.01 g of 3-(4-fluorophenyl)-1-isopropyl-1H-indole, 0.92 g of methyl 3,3-dimethoxypropionate, 0.72 mL of 90 wt% aqueous acetic acid 20 (containing 4 mmol of water) and 6 mL of glacial acetic acid were mixed, then, 0.33 g of phosphorus oxychloride was added dropwise into the mixture at an inner temperature of 25°C, the added mixture was stirred for 9 hours at the same temperature to cause a reaction. After completion of the reaction, 16 mL of water was added dropwise into the 25 reaction liquid, and the precipitated crystals were filtrated. The crystals were washed with 20 vol% aqueous methanol, then, dried to obtain 1.25 g of methyl trans-3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylate (yellow solid). Yield: 93%.

¹H-NMR (d/ppm, CDCl₃, 400 MHz)

1.70 (6H, d, J=7 Hz), 3.76 (3H, s), 4.95 (1H, m), 5.96 (1H, d, J=16 Hz), 7.50 (1H, d, J=8 Hz), 7.57 (1H, d, J=8 Hz), 7.08 to 7.40 (6H, m), 7.82 (1H, d, J=16 Hz)

5 Example 2

1.04 g of 1-methyl-2-phenyl-1H-indol, 0.64 g of methyl trans-3-methoxyacrylate, 94.5 mg of water and 6 mL of glacial acetic acid were mixed, 124 mg of phosphorus oxychloride was added into the mixture at an inner temperature of 25°C , the added mixture was stirred
10 for 7 hours at the same temperature to cause a reaction. After completion of the reaction, 30 mL of water was added dropwise into the reaction liquid, 50 mL of ethyl acetate was added and extraction treatment was conducted, and the resulting organic layer was subjected to concentration treatment. The resultant concentrated residue was
15 purified by flash chromatography, to obtain 1.11 g of methyl trans-3-(1-methyl-2-phenyl-1H-indol-3-yl)acrylate (yellow solid).
Yield: 76%.

¹H-NMR (d/ppm, CDCl₃, 400 MHz)

3.64 (3H, s), 3.74 (3H, s), 6.46 (1H, d, J=16 Hz), 7.29 to 7.55 (9H, m), 7.72 (1H, d, J=16 Hz)

Example 3

1.68 g of 1,3,5-trimethoxybenzene, 2.32 g of methyl trans-3-methoxyacrylate, 0.18 g of water and 6 mL of glacial acetic acid
25 were mixed, 164 mg of phosphorus oxychloride was added into the mixture at an inner temperature of 25°C , the added mixture was stirred for 3 hours at the same temperature to cause a reaction. After completion of the reaction, 36 mL of water was added dropwise into the reaction liquid, and the precipitated crystals were filtrated. The

crystals were washed with 20 vol% of aqueous methanol, then, dried to obtain 2.28 g of methyl trans-3-(2,4,6-trimethoxyphenyl)acrylate (white solid). Yield: 91%.

¹H-NMR (d/ppm, CDCl₃, 400 MHz)

5 3.79 (3H, s), 3.85 (3H, s), 3.87 (6H, s), 6.12 (2H, s), 6.76 (1H, d, J=16 Hz), 8.08 (1H, d, J=16 Hz)

Example 4

1.7 g of 1,3,5-trimethoxybenzene, 1.68 g of methyl

10 3,3-dimethoxypropionate and 12 mL of glacial acetic acid were mixed, 313 mg of 35 wt% hydrochloric acid was added into the mixture at an inner temperature of 25°C, the added mixture was stirred for 1 hour at the same temperature to cause a reaction. After completion of the reaction, 36 mL of water was added dropwise into the reaction liquid, 15 and the precipitated crystals were filtrated. The crystals were washed with 20 vol% of aqueous methanol, then, dried to obtain 2.46 g of methyl trans-3-(2,4,6-trimethoxyphenyl)acrylate (white solid). Yield: 98%.

Example 5

20 1.68 g of 1,2,3-trimethoxybenzene, 1.34 g of methyl trans-3-methoxyacrylate and 6 mL of glacial acetic acid were mixed, 313 mg of 35 wt% hydrochloric acid was added into the mixture at an inner temperature of 25°C, the added mixture was stirred for 16 hours at the same temperature to cause a reaction. After completion of the reaction, 25 30 mL of water and 50 mL of ethyl acetate were added into the reaction liquid, and extraction treatment was conducted. The resultant organic layer was washed with water, then, concentrated, and the resultant concentrated residue was purified by silica gel column chromatography (developing liquid: n-heptane/ethyl acetate = 6/1 to 5/1), to obtain 0.63 g

of methyl trans-3-(2,3,4-trimethoxyphenyl)acrylate (white solid). 0.92 g of the raw material 1,2,3-trimethoxybenzene was recovered. The yield of methyl 3-(2,3,4-trimethoxyphenyl)acrylate based on the converted 1,2,3-trimethoxybenzene was 55%.

5 ¹H-NMR (d/ppm, CDCl₃, 400 MHz)
3.80 (3H, s), 3.88 (3H, s), 3.89 (3H, s), 3.92 (3H, s), 6.42 (1H, d, J=16 Hz), 6.69 (1H, d, J=9 Hz), 7.26 (1H, d, J=9 Hz), 7.88 (1H, d, J=16 Hz)

10 Example 6

The reaction and post treatment were conducted in the same manner as in Example 5 except that 1.54 g of 2,6-dimethoxyphenol was used instead of 1.68 g of 1,2,3-trimethoxybenzene, to obtain 0.76 g of methyl trans-3-(3-hydroxy-2,4-dimethoxyphenyl)acrylate (white solid). Yield:
15 32%.

1 ¹H-NMR (d/ppm, CDCl₃, 400 MHz)
3.80 (3H, s), 3.91 (3H, s), 3.93 (3H, s), 5.58 (1H, s), 6.45 (1H, d, J=16 Hz), 6.67 (1H, d, J=9 Hz), 7.07 (1H, d, J=9 Hz), 7.87 (1H, d, J=16 Hz)

20

Example 7

2 Into a solution prepared by dissolving 0.63 g of 3-(4-fluorophenyl)-1-isopropyl-1H-indole in 3 mL of dichloromethane was added dropwise 0.77 g of phosphorus oxychloride at an inner temperature of 0 to 10°C, then, 0.92 g of trans-3-methoxyacrylonitrile was added dropwise. Then, the mixture was stirred overnight at room temperature to cause a reaction, further, the mixture was reacted for 6 hours at the reflux temperature. After completion of the reaction, the reaction liquid was added into 100 mL of 5 wt% aqueous sodium

hydrogen carbonate, and extracted with ethyl acetate three times. The resulting organic layers were combined and washed with water, then, dried with anhydrous magnesium sulfate. The magnesium sulfate was filtrated off, and the resulting filtrate was concentrated to obtain a

5 concentrated residue containing

3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylonitrile (trans-cis isomer mixture containing mainly trans isomer). The resulting concentrated residue was purified by silica gel column chromatography (developing liquid: n-heptane/ethyl acetate: 10/1 to 5/1) to obtain 0.34 g

10 of trans-3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylonitrile (yellow solid). Yield: 45%

¹H-NMR (d/ppm, CDCl₃, 400 MHz)

1.70 (6H, d, J=7 Hz), 4.85 (1H, m), 5.35 (1H, d, J=16 Hz), 7.09 to 7.46 (7H, m), 7.55 (1H, d, J=8 Hz), 7.48 (1H, d, J=16 Hz)

15

Example 8

0.62 g of 3-(4-fluorophenyl)-1-isopropyl-1H-indole, 0.57 g of methyl trans-3-methoxyacrylate, 46 mg of water and 6.4 mL of glacial acetic acid were mixed, then, 66 mg of phosphorus oxychloride was

20 added dropwise into the mixture at an inner temperature of 25°C, the added mixture was stirred for 21 hours at the same temperature to cause a reaction. After completion of the reaction, the same post treatment was conducted as in Example 1 to obtain 0.65 g of methyl trans-3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylate (yellow

25 solid). Yield: 79%.

Example 9

The reaction and post treatment were conducted in the same manner as in Example 8 except that the amount of phosphorus oxychloride was

164 mg and the reaction time was 9 hours, to obtain 0.79 g of methyl trans-3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylate (yellow solid). Yield: 96%.

5 Examples 10 to 13

The reaction and post treatment were conducted in the same manner as in Example 8 except that acids shown in Table 1 were used instead of phosphorus oxychloride, the amount of glacial acetic acid was 6 mL and conditions shown in Table 1 were used, to obtain methyl

- 10 trans-3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylate (yellow solid). The results are shown in Table 1.

Table 1

Example	Acid (mg)	Water	Reaction time	Yield
10	99 wt% sulfuric acid (156)	46mg	15Hr	59%
11	35 wt% hydrochloric acid (166)	108mg (water in hydrochloric acid)	15Hr	94%
12	p-toluenesulfonic acid monohydrate (302)	56mg (containing 10 mg of crystal water)	15Hr	74%
13	47 wt% aqueous hydrobromic acid (274)	145mg water in aqueous hydrobromic acid	5Hr	90%

15 Example 14

0.31 g of 3-(4-fluorophenyl)-1-isopropyl-1H-indole, 0.28 g of methyl trans-3-methoxyacrylate, 36 mg of water and 6 mL of acetonitrile were mixed, then, 164 mg of phosphorus oxychloride was added dropwise into the mixture at an inner temperature of 25°C, the added

mixture was stirred for 22 hours at the same temperature to cause a reaction. After completion of the reaction, the same post treatment was conducted as in Example 1 to obtain 0.21 g of methyl trans-3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylate (yellow solid). Yield: 51%.

Example 15

2.53 g of 3-(4-fluorophenyl)-1-isopropyl-1H-indole, 2.32 g of methyl trans-3-methoxyacrylate, 0.3 g of water and 15 mL of acetonitrile were mixed, then, 2.51 g of phosphorus oxychloride was added dropwise into the mixture at an inner temperature of 25°C, the added mixture was stirred for 19 hours at the same temperature to cause a reaction. After completion of the reaction, the same post treatment was conducted as in Example 1 to obtain 2.17 g of methyl trans-3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylate (yellow solid). Yield: 65%.

Examples 16 to 18

The reaction and post treatment were conducted in the same manner as in Example 14 except that the use amounts of phosphorus oxychloride and water were as shown in Table 2 and the reaction time was 18 hours, to obtain methyl trans-3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylate (yellow solid). The results are shown in Table 2.

Table 2

Example	Use amount of phosphorus oxychloride (mg)	Use amount of water (mg)	Yield
16	242	44	56%
17	398	44	75%
18	348	0	32%

Examples 19 to 20

The reaction and post treatment were conducted in the same manner as in Example 14 except that acids shown in Table 3 were used instead of phosphorus oxychloride and the reaction time was 19 hours, to obtain methyl trans-3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylate (yellow solid). The results are shown in Table 3.

Table 3

Example	Acid (mg)	Yield
19	boron trifluoride•tetrahydrofuran complex (348)	27%
20	99 wt% sulfuric acid (119)	39%

Example 21

1.27 g of 3-(4-fluorophenyl)-1-isopropyl-1H-indole, 1.16 g of methyl trans-3-methoxyacrylate and 12 mL of glacial acetic acid were mixed, then, 797 mg of 30 wt% hydrogen bromide/acetic acid solution was added dropwise into the mixture at an inner temperature of 25°C, the mixture was stirred for 5 hours at the same temperature to cause a reaction. After completion of the reaction, the same post treatment was conducted as in Example 1 to obtain 0.15 g of methyl trans-3-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]acrylate (yellow solid).

Yield: 8%.

Example 22

20 1.27 g of 3-(4-fluorophenyl)-1-isopropyl-1H-indole, 1.32 g of 1,1-dimethoxy-3-butanone and 6 mL of formic acid were mixed, then, 0.78 g of 30 wt% hydrogen bromide/acetic acid solution was added into the mixture at room temperature, the added mixture was stirred for 19 hours at the same temperature to cause a reaction. After completion of the reaction, 50 mL of ethyl acetate and 20 mL of water were added and extraction treatment was conducted, the resulting organic layers were

washed with water, then, dried with anhydrous magnesium sulfate. The magnesium sulfate was filtrated, then, the resulting filtrate was concentrated, to obtain a concentrated residue containing trans-4-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]-3-buten-2-one.

- 5 The concentrated residue was purified by silica gel chromatography (developing liquid: n-heptane/ethyl acetate: 4/1) to obtain 0.72 g of trans-4-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]-3-buten-2-one (yellow solid). Yield: 52%. 0.18 g of the raw material 3-(4-fluorophenyl)-1-isopropyl-1H-indole were recovered together.

10 $^1\text{H-NMR}$ (d/ppm, CDCl_3 , 400 MHz)

1.71 (6H, d, $J=7$ Hz), 2.23 (3H, s), 4.94 (1H, m), 6.29 (1H, d, $J=16$ Hz), 7.09 to 7.40 (6H, m), 7.49 (1H, $J=8$ Hz), 7.51 (1H, $J=8$ Hz), 7.66 (1H, d, $J=16$ Hz)

15 Example 23

1.27 g of 3-(4-fluorophenyl)-1-isopropyl-1H-indole, 1.32 g of 1,1-dimethoxy-3-butanone and 6 mL of acetic acid were mixed, then, 260 mg of 35 wt% hydrochloric acid was added into the mixture at room temperature, the added mixture was stirred for 18 hours at the same 20 temperature to cause a reaction. After completion of the reaction, two drops of the reaction liquid were sampled. The sampled liquid was concentrated under reduced pressure, and the resulting concentration residue was dissolved in chloroform-d, and $^1\text{H-NMR}$ spectrum was measured to find that the above-mentioned concentrated residue 25 contained trans-4-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]-3-buten-2-one and the raw material, 3-(4-fluorophenyl)-1-isopropyl-1H-indole and that the content ratio thereof (trans-4-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]-3-buten-2-one/ 3-(4-fluorophenyl)-1-isopropyl-1H-indole (calculated from NMR

integral value)) was 1/2.7.

Example 24

2.07 g of 1-methyl-2-phenyl-1H-indole, 1.32 g of

5 1,1-dimethoxy-3-butanone and 12 mL of acetic acid were mixed, then,
313 mg of 35 wt% hydrochloric acid was added into the mixture at room
temperature, the added mixture was stirred for about 14 hours at the
same temperature to cause a reaction. At a time point about 10 minutes
after starting of stirring and reaction, blue solid precipitated to render
10 stirring difficult. Therefore, 8 mL of acetic acid was added. After
completion of the reaction, 60 mL of water was added dropwise, and the
precipitated crystals were filtrated. The crystals were washed with 10
vol% methanol/water, then, dried to obtain 2.44g of trans-4-[1-methyl-
2-phenyl-1H-indol-3-yl]-3-buten-2-one (blue green solid). Yield: 89%.

15 $^1\text{H-NMR}$ (d/ppm, CDCl_3 , 400 MHz)

2.24 (3H, s), 3.65 (3H, s), 6.83 (1H, d, $J=16$ Hz), 7.30 to 7.43 (5H,
m), 7.52 to 7.59 (4H, m), 8.02 (1H, $J=8$ Hz)

The method of the present invention is a method of higher atom

20 economy capable of producing an aromatic unsaturated compound which
can be derived into medical and agricultural chemicals and the like
without using an aromatic halide manifesting high load on environments
as a raw material and without by-producing a hydrogen halide needing
neutralization. Further, the method of the present invention is more
25 advantageous also from industrial standpoint since a transition metal
which is expensive and requires complicated post treatment is not used.